Title
NCMP-16. THE ROLE OF p38 AND JNK MAPK PATHWAYS IN CISPLATIN CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENT

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Aspergillus fumigatus. No recurrent tumor was present. Given the lack of perceived risk factors, further questioning of the patient and her mother disclosed that precisely 1 year prior to surgery she and her family had participated in "cleaning out an old very dirty and dusty barn" in southern Colorado without the use of face masks; only the proband experienced sequelae. Anti-fungal therapy (voriconazole) was recommended although patient use was intermittent and symptoms have progressed. CONCLUSION: Community-acquired Aspergillus infections due to exposure to silage or barn detritus contaminated by fungal hyphae is almost never seen today, in comparison to opportunistic infections due to known risk factors of neutropenia and/or steroid usage. Replacement therapy may have added to this patient's risk. Infections all too often mimic recurrent tumor.

NCMP-15. CNS LYMPHOMA: THE GREAT MIMICKER

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INTRODUCTION: Primary central nervous system lymphoma (PCNSL) is a variant of non-Hodgkin lymphoma, affecting the brain, leptomeninges, eyes, and spinal cord. PCNSL is a progressive disease with symptom onset occurring over weeks that presents with varied signs and symptoms, including focal neurological deficits, mental status changes, behavioral changes and seizures. Tissue diagnosis is imperative, though MRI, ophthalmologic and CSF evaluation can aid in diagnosis. PET scan and bone marrow biopsy are important for assessing metastatic spread following diagnosis. CASE PRESENTATION: We present a case series, comprised of three patients with atypical presentations of CNS lymphoma. Patient 1. 64 year old male presented with facial muscle weakness, vertigo, and diplopia. Initial MRI showed an old thalamic and new internal capsule infarcts. EMG suggested sensorimotor peripheral neuropathy consistent with Guillain-Barre Syndrome, leading to treatment with a five day course of IVIG. His MRI findings gradually worsened, ultimately revealing leptomeningeal enhancement of the bilateral vestibulococchlear nerves, facial nerves and the trigeminal nerves. Patient 2. 66 year old male with a past medical history of primary cutaneous anaplastic T cell lymphoma stage 1 EA, status post field radiation, presented with aphasia and ataxia. Brain MRI showed extensive, enhancing hyperdensities in the midbrain, suggestive of multiple sclerosis, prompting treatment with steroids. He continued to clinically worsen, prompting tissue diagnosis. Patient 3. 66 year old male presented with recurrent syncopal episodes and aphasia, found to have a 4 cm extra axial mass in the left temporal region on MRI suggestive of a meningioma. CONCLUSION: All three patients eventually underwent brain biopsy with a final histologic diagnosis of PCNSL. Due to the highly variable initial presentation of this condition and the wide range of pathologies it mimics, CNS lymphoma should be included in the differential diagnosis of patients presenting with atypical neuroimaging or clinical findings.

NCMP-16. THE ROLE OF P38 AND JNK MAPK PATHWAYS IN CISPLATIN CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENT

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OBJECTIVES: Chemotherapy-related cognitive impairment (CRCI) is an adverse sequela of cancer treatment commonly reported in cancer survivors. Cisplatin is used for the treatment of various malignancies including ovarian, testicular, head and neck cancers, and pediatric brain tumors. More than 30% of advanced ovarian cancer patients develop CRCI during and after platinum-based chemotherapy. We examined the role of p38 and c-Jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK) activation in cisplatin-induced CRCI, and whether the small molecule p38 MAPK inhibitor Neflamapimod and JNK inhibitor SP600125, can prevent cisplatin-induced neuronal damage. The p38 and JNK MAPK signaling pathways are involved in various stress response pathways in the CNS including oxidative stress. METHODS: The effect of cisplatin on cognition in an ovarian cancer female rat model was assessed by novel object recognition (NOR). Hippocampal glutathione levels were measured post-behavioral testing. P38 and JNK MAPK signaling activation were assessed in the neural cell lines PC12 and SH-SY5Y by Western blot. Cultured hippocampal neurons were pretreated with Neflamapimod or SP600125 followed by cisplatin for 24 hours, and dendritic spine density and branch length were quantified. RESULTS: Cisplatin increased phospho-p38 and phospho-JNK MAPK protein levels in PC12 and SH-SY5Y cells. Cisplatin reduced dendritic branching and spine density, which was prevented by Neflamapimod and SP600125 pre-treatment in hippocampal neurons, *in vitro*. Chronic cisplatin treatment decreased hippocampal glutathione levels and impaired cognitive function in the ovarian cancer rat model. DISCUSSION: The cognitive deficits caused by cisplatin results in part from dendritic damage and neural apoptosis, which is mediated by oxidative stress and the p38 and JNK MAPK pathways. P38 and JNK MAPK inhibition mitigated cisplatin-induced dendritic spine loss and branching *in vitro*. Next, we will examine whether Neflamapimod and SP600125 administration in an ovarian cancer rat model is safe and if they can prevent cognitive impairment.

NCMP-17. MISMATCH REPAIR MUTATIONS AND THE CENTRAL NERVOUS SYSTEM: A CASE SERIES OF GERMLINE MUTATIONS AND CNS MALIGNANCY

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Our understanding of genetic predispositions for malignancy is continually evolving. One family of germline mutations well described in the literature is that of the DNA mismatch repair mechanism (MMR). Lynch syndrome (LS) is due to a loss of function mutation of several MMR genes- MSH2, MLH1, MSH6, and PMS2. Germline MMR mutations lead to microsatellite instability and loss of genomic integrity resulting in an increased risk for various cancers (colorectal, genitourinary, etc). LS may be as common as 1 in 400 people and some MMR mutations have been associated with gliomas. There is a paucity of information regarding frequency of glioma subtypes as well as tumor genetic and molecular characteristics which have important clinical implications. We describe a case series of 6 individuals with germline MMR mutations and brain tumors. Those with MSH2 and PMS2 mutations (n=3) developed glioblastomas at a mean age at diagnosis of 48 years. These tumors expressed MGMT hyper-methylation and high tumor mutational burden. Only one had IDH-1 mutation. Those with MLH1 mutations (n=3), did not develop gliomas. This raises the question of differential glioma subtype development based on MMR gene. It also highlights the possibility of Lynch-associated gliomas having more favorable treatment response due to MGMT methylation and potential response to immunotherapy based on high tumor mutational burden. Though the sample size is small, there appears to be a preponderance of women compared to men (5:1 respectively). Larger studies are needed to verify CNS involvement in germline MMR mutations. In doing so, we hope to identify factors that may influence clinical management and lead to a better understanding of treatment response and disease prognosis.

NCMP-18. NEUROTOXICITY AS A POTENTIAL SURROGATE MARKER FOR THERAPEUTIC RESPONSE WITH COMMERCIAL ANTI-CD19 CAR T-CELL THERAPY

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Neurotoxicity is a common occurrence and a major form of morbidity in adult patients with relapsed or refractory (R/R) diffuse large B cell lymphoma (DLBCL) patients treated with anti-CD19 directed chimeric antigen receptor (CAR) T-cell therapy. Variables related to the incidence and severity of neurotoxicity have been relatively well delineated, but the association between neurotoxicity and the efficacy of CAR T-cell therapy has not been well studied. We performed a retrospective analysis of the outcomes of DLBCL patients who developed neurotoxicity following anti-CD19 CAR T-cell treatment. The analysis included 26 patients with R/R DLBCL who received commercial anti-CD19 CAR T-cell therapy. All patients received a lymphodepleting chemotherapy regimen consisting of fludarabine and cyclophosphamide. Twenty-five patients received axicabtagene ciloleucel, and 1 received tisagenlecleucel. The overall incidence of neurotoxicity was 88%; 31% developed severe neurotoxicity (Grade III-IV by CTCAE). Higher neurotoxicity was associated with better PFS by both CTCAE (CR 2.4 ± 1.1 vs. PD 1.4 ± 1.3, p = 0.051) and CARTOX-10 (CR 3.78 ± 4.6 vs. PD 7.7 ± 3.8, p = 0.044) grading systems. Higher neurotoxicity continued to show a trend at 6, 9, and 12 months by the CTCAE grading system (CR 2.4 ± 1.0 vs. PD 1.7 ± 1.3, p = 0.085), and no patients had disease recurrence after 6 months. In this limited cohort, neurotoxicity severity was paradoxically positively correlated with progression-free survival with commercial CAR T-cell therapy and may therefore indicate an effective therapeutic response.

NCMP-19. SIDE EFFECTS FROM CHEMOTHERAPY VERSUS SYMPTOMS FROM COVID-19 INFECTION

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INTRODUCTION: Adverse effects from chemotherapy such as high dose methotrexate (HD-MTX) are seen during and after chemotherapy. During this coronavirus disease 2019 (COVID-19) pandemic period, COVID-19 infection symptoms following chemotherapy due to immune compromise could mimic chemotherapy associated side effects. Differentiation on time is needed for correct management. CASE REPORT: A 50-year old male with clinical history of ocular lymphoma underwent HD-MTX therapy.